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A semi-automated algorithm for hypothalamus volumetry in 3 Tesla magnetic resonance images

Julia Wolff[a], Stephanie Schindler[a], Christian Lucas[a], Anne-Sophie Binninger[a], Luise Weinrich[a], Jan Schreiber[a], Ulrich Hegerl[a], Harald E. Möller[b], Marco Leitzke[d], Stefan Geyer[c,1], Peter Schönknecht[1,a,*]

[a] Department of Psychiatry and Psychotherapy, Leipzig University Hospital, Leipzig, Germany
[b] Methods and Development Group "Nuclear Magnetic Resonance", Max Planck Institute for Human Cognitive and Brain Sciences, Leipzig, Germany
[c] Department of Neurophysics, Max Planck Institute for Human Cognitive and Brain Sciences, Leipzig, Germany
[d] Department of Anesthesiology, Helios Clinics, Leisnig, and Jena University Hospital, Germany

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ABSTRACT

The hypothalamus, a small diencephalic gray matter structure, is part of the limbic system. Volumetric changes of this structure occur in psychiatric diseases, therefore there is increasing interest in precise volumetry. Based on our detailed volumetry algorithm for 7 Tesla magnetic resonance imaging (MRI), we developed a method for 3 Tesla MRI, adopting anatomical landmarks and work in triplanar view. We overlaid T1-weighted MR images with gray matter-tissue probability maps to combine anatomical information with tissue class segmentation. Then, we outlined regions of interest (ROIs) that covered potential hypothalamus voxels. Within these ROIs, seed growing technique helped define the hypothalamic volume using gray matter probabilities from the tissue probability maps. This yielded a semi-automated method with short processing times of 20–40 min per hypothalamus. In the MRIs of ten subjects, reliabilities were determined as intraclass correlations (ICC) and volume overlaps in percent. Three raters achieved very good intra-rater reliabilities (ICC 0.82–0.97) and good inter-rater reliabilities (ICC 0.78 and 0.82). Overlaps of intra- and inter-rater runs were very good (≥ 89.7%). We present a fast, semi-automated method for *in vivo* hypothalamus volumetry in 3 Tesla MRI.

1. Introduction

Since the rise of neuroanatomy, we have learned that the hypothalamus is a small but important gray matter brain region of the diencephalon (Le Gros Clark, 1935). As part of the limbic system it connects the cerebral cortex with the visceral neural system and regulates basic physiological functions such as stress reaction (Herman et al., 2003; McEwen, 2007), hormone circuits (Addison and Rissman, 2012; Fliers et al., 2014; Murray et al., 2015), appetite (Suzuki et al., 2010; Valassi et al., 2008) and the circadian rhythm (Saper et al., 2005; Wood and Loudon, 2014).

Many of these functions are affected in psychiatric diseases, suggesting an involvement of the hypothalamus; whether its role is cause or result often remains to be discussed. Hyperactivity of the hypothalamus-pituitary-adrenal (HPA) axis has been observed in depressed patients (Bao et al., 2008), in major depression (Arborelius et al., 1999) as well as bipolar disorder (Belvederi et al., 2016). It seems to be sensitized by childhood trauma, leading to a higher risk for developing depression (Heim et al., 2008). Evidence also suggests alterations of HPA axis activity in schizophrenia (Bradley and Dinan, 2010) and borderline personality disorder (Wingenfeld et al., 2010). Besides psychiatric research, chronic pain syndromes and the common therapeutic approaches towards them such as nonsteroidal anti-inflammatory drugs and opioids in long term use, are connected with dysfunction of the HPA axis (Aloisi et al., 2011; Arkink et al., 2016). Also, hypothalamic alterations have been described in amyotrophic lateral sclerosis and Huntington's disease (Gabery et al., 2015; Gorges et al., 2017). Research went on to focus on the hypothalamus itself. Post-mortem studies in patients with depression showed a smaller hypothalamic volume (Baumann and Bogerts, 2001; Bielau et al., 2005) and a reduction of neuron number in the paraventricular but not the supraoptic nucleus (Manaye et al., 2005).

Nevertheless, to date the actual size of the hypothalamus in healthy humans is critically discussed. Nieuwenhuys et al. described the

* Corresponding author.
E-mail address: peter.schoenknecht@medizin.uni-leipzig.de (P. Schönknecht).
[1] Both authors contributed equally.

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hypothalamus volume to be 4000 mm^3 (Nieuwenhuys et al., 2008), histological studies estimated the human hypothalamus to be smaller (ranging from 1320 mm^3 to 3560 mm^3), but several neuroimaging studies reported rather half this size with volumes between 600 mm^3 and 1050 mm^3 for bilateral hypothalami (reviewed in Schindler et al., 2013).

The definition of the hypothalamic region is challenging and may have caused the significant differences between the studies. Le Gros Clark divided the hypothalamus into four rostro-caudal divisions: preoptic, anterior, tuberal and mamillary (Le Gros Clark, 1935). In fact, the preoptic area is of telencephalic origin, but since there are strong functional connections to the hypothalamus, it is included as an own hypothalamic section (Le Gros Clark, 1935; Lemaire et al., 2011; Nieuwenhuys et al., 2008). Important macrostructural boundaries include the lamina terminalis and anterior commissure (AC) anteriorly, the third ventricle medially, the hypothalamic sulcus and fornix superiorly, the optic tract, substantia innominata, internal capsule and cerebral peduncle laterally, and the mamillary bodies (MB) posteriorly. Whether to in- or exclude the latter is handled differently among work groups. Accordingly, the posterior margin is set rostral or caudal of the MB. The optic chiasm, hypophyseal stalk and cerebral exterior form the inferior margin. These anatomical landmarks (including the MB) are commonly implemented by several work groups when measuring the hypothalamic volume (Gabery et al., 2015; Goldstein et al., 2007; Ha et al., 2013; Klomp et al., 2012; Makris et al., 2013; Tognin et al., 2012). However, the hypothalamus is surrounded by a variety of smaller gray and white matter structures (Mai et al., 2008; Riley, 1943) and, with increasing resolution of magnetic resonance imaging (MRI), more details of them become visible. Therefore, attention should be paid to the diagonal band of Broca and the medial forebrain bundle in the preoptic area, the zona incerta in the tuberal hypothalamus and to the subthalamic nucleus and substantia nigra in the posterior (or mamillary) hypothalamus (Schindler et al., 2013).

An often neglected issue is the variability in MRI signal intensity within the hypothalamus due to different distribution of gray and white matter rostro-caudally. Lemaire et al. analyzed the distribution of white matter connections from the hypothalamus to other brain areas (Lemaire et al., 2011). Diffusion tensor imaging (DTI) tractography displayed WM fascicles made up of axons running in the same direction. They subdivided the hypothalamus into six compartments and listed number and destination of white matter connections per compartment for each of their 14 subjects. Applied to our sections, there is lower white matter connectivity in the preoptic hypothalamus (equaling Lemaire's preoptic and supraoptic compartments) than in the anterior, tuberal and posterior section (Lemaire's anteroventral, anterodorsal, lateral and posterior compartment). Miller et al. described the MRI signal of mamillary bodies to be “intermediate between white matter tracts and hypothalamic nuclei”, thus higher than the rostral sections. This may be due to white matter connections to or from the mamillary bodies such as the fornix, the principal mamillary fasciculus or the supramamillary commissure (Mai et al., 2008; Naidich et al., 2009; Riley, 1943).

The basis of the method presented here is the manual computer-assisted algorithm for volumetry of the hypothalamus in 7 T MRI by Schindler et al. (2013). Novelties include work in triplanar view, i.e. in coronal, horizontal and sagittal views simultaneously, and the use of color coding for distinguishing the hypothalamus from other tissues. Other work groups applied their manual volumetry methods to MRI data acquired on 1.5 T scanners with lower spatial resolution (Klomp et al., 2012; Pol et al., 2006). These studies used T1-weighted images only in coronal views and without correction for brightness and contrast. Inter-rater reliabilities were not reported.

Another approach for the investigation of hypothalamic volume differences is voxel based morphometry (VBM). This method compares tissue probability maps (TPMs) to detect regional volumetric differences between study groups in a whole-brain-analysis. Two groups performed VBM analysis finding a positive correlation between hypothalamic volume and self-esteem (Agroskin et al., 2014) and a negative correlation with waist circumference (Kurth et al., 2013). However, VBM is not suited for precise volumetry of a structure, as it does not determine exact volumes. Further studies developed fully automated methods combining TPMs from Statistical parametric mapping (SPM) with ready-made regions of interest (ROIs) from the WFU pickatlas (www.fmri.wfubmc.edu/software/pickatlas) to assess hypothalamus volumes (Kuhlmann et al., 2013). Another approach was FreeSurfer segmentation (Marqués-Iturria et al., 2013) which, however, is not a segmentation of the hypothalamus alone but of the entire ventral diencephalon (www.freesurfer.net/).

Two groups performed semi-automated volumetry of the hypothalamus so far, both with 1.5 T MRI. Goldstein et al. developed a segmentation procedure based on the nadir between gray and white matter peaks in histograms (Filipek et al., 1994; Goldstein et al., 2007) and manually defined landmarks that helped to parcellate the segmentation into substructures (Goldstein et al., 2007). Ha and colleagues used TPMs for gray matter (GM) and cerebrospinal fluid (CSF) from SPM and cuboid-shaped ROIs for volumetry of the hypothalamus (Ha et al., 2013). Anatomical delineation of the hypothalamus was left to the TPM, gray matter structures adjoining the hypothalamus that lay inside the rather crude ROI were not specifically excluded.

Except for the 7 T MRI algorithm (Schindler et al., 2013), none of these studies used triplanar views for anatomical validity or respected different ranges of T1-weighted signals among the sections of the hypothalamus. Anatomical precision is variable among the other published methods, structures like the hypothalamic sulcus as superior boundary or adjoining gray matter structures like the olfactory tubercle, zona incerta, substantia nigra or subthalamic nucleus were not or not completely taken into consideration.

The aim of this study was to develop a semi-automated algorithm for hypothalamus volumetry in 3 T MRI data. It adopts the strengths of the computer assisted algorithm for 7 T MRI: detailed anatomical landmarks for work in triplanar view. Beyond that, gray matter tissue probability maps and seed growing technique automate part of the work flow to make it more objective, easier and faster.

2. Methods

2.1. Sample

The test sample of ten subjects for this study was selected from a group of 84 subjects with the following characteristics: 33 males, 51 females, aged 38.5 ± 12.2 years; 23 subjects were healthy controls, 41 patients with major depression (21 medicated, 20 not medicated), 20 with bipolar depression (all medicated). We randomly chose four healthy controls and three subjects with uni- and bipolar depression, respectively. Five patients were medicated with antidepressants at the time of image acquisition. The test subset were six females, four males, age 38.3 ± 13.2 years, all right handed. Healthy subjects and patients were recruited at the Max Planck Institute for Human Cognitive and Brain Sciences and the Department of Psychiatry and Psychotherapy of the University Hospital in Leipzig, respectively. The study was approved by the Ethics Committee of the University of Leipzig, all subjects had given written informed consent.

2.2. MR image acquisition and preprocessing

MR images were acquired with a 3 T MR scanner (MAGENTOM TIM Trio, Siemens Healthcare, Erlangen, Germany). We used a 32-channel head coil and a 3D magnetization-prepared rapid gradient echo (MP-RAGE) sequence, repetition time (TR) was 1300 ms, echo time (TE) 3.46 ms, inversion time (TI) 650 ms and flip angle 10°. The 3D volumes had 256 × 240 × 176 isotropic voxels of 1 mm^3. Acquisition time was 10:26 min.